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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
ROSARIO LIZIO, ET AL.	: EXAMINER: WESTERBERG, N. M.
SERIAL NO: 10/564,096	:
FILED: MAY 2, 2006	: GROUP ART UNIT: 1618

FOR: MULTIPARTICLE PHARMACEUTICAL DOSAGE FORM CONTAINING A MUCOADHESIVELY FORMULATED PEPTIDE OR PROTEIN ACTIVE SUBSTANCES METHOD FOR PRODUCING SAID PHARMACEUTICAL DOSAGE FORM

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

APPEAL BRIEF

This is an appeal to the Board of Patent Appeals and Interferences (hereafter Board) under 35 U.S.C. § 134 from the June 22, 2009, rejections of Claims 1, 3, 4, 6-11, and 33-35 of Application 10/564,096, filed May 2, 2006. A Notice of Appeal was timely filed on September 22, 2009, with no request for extension of time. This Appeal Brief is timely filed on November 23, 2009, with no extension of time.

STATEMENT OF REAL PARTY OF INTEREST

The real party of interest in this appeal is EVONIK ROEHM GmbH, Darmstadt, Germany.

STATEMENT OF RELATED APPEALS AND INTERFERENCES

Appellant/Applicant, Appellant/Applicant's legal representative, and Appellant/Applicant's assignees, are aware of no appeals, interferences, or judicial proceedings that are related to, directly affect or would be directly affected by, or have a bearing on the Board's decision of the Board in this appeal.

STATEMENT OF JURISDICTION

The Board has jurisdiction of the twice rejected claims on appeal under 35 U.S.C. § 134. This is an appeal to the Board from the June 22, 2009, taken from twice rejected Claims 1, 3, 4, 6-11, and 33-35 of Application 10/564,096, filed May 2, 2006. A Notice of Appeal was timely filed on September 22, 2009, with no request for extension of time. This Appeal Brief is timely filed on November 23, 2009, with no extension of time.

STATUS OF THE CLAIMS

Claims 1, 3, 4, 6-11, and 33-35 stand twice rejected under 35 U.S.C. § 103. The rejections are APPEALED.

Claim 34 stands twice rejected under 35 U.S.C. § 102. The rejection is APPEALED.

Claims 33 and 34 stand twice rejected under 35 U.S.C. § 112, 1st ¶ (written description requirement). The rejections are APPEALED.

Claims 1, 3, 4, 6-11, and 33-35 are APPEALED.

Claims 2, 5 and 12-32 have been withdrawn from consideration by the Examiner.

The Claims Appendix to this Appeal Brief provides a clean copy of all pending claims.

STATUS OF AMENDMENTS

No amendment to Claims 1, 3, 4, 6-11, and 33-35 has been submitted or entered after the Examiner's June 22, 2009, rejections thereof.

SUMMARY OF THE CLAIMED SUBJECT MATTER

The claims are directed to a pharmaceutical form comprising pellets having a size of 50 to 2,500 μm (Spec., p. 4, ll. 22-24). The pellets enable superior delivery, distribution and release of an active substance to and in the intestine (Spec., p. 4, l. 20, to p. 6, l. 4). The enabling pellets comprise "an inner matrix layer consisting essentially of" an active peptide or protein substance embedded in (Claims Appendix, Claim 1), or "an inner matrix comprising" an active ingredient and (Claims Appendix, Claim 34), a polymer having a mucoadhesive effect (Spec., p. 4, ll. 26-32; p. 5, ll. 31-37; and 34), e.g. chitosan (Spec., p. 12, ll. 10-24). The inner matrix layer is coated with an "outer film coating consisting essentially of an anionic polymer or copolymer" (Spec., p. 4, ll. 34-37; p. 6, ll. 1-4; Claims Appendix, Claims 1 and 34), e.g. Eudragit® L/S/FS type copolymers of methyl/ethyl (meth)acrylate and (meth)acrylic acid (Spec., p. 16, l. 4, to p. 21, l. 12).

The outer film protects the inner matrix layer consisting essentially of the active peptide or protein and the mucoadhesive polymer having a mucoadhesive effect (Claim 1), or the inner matrix comprising the active agent and the polymer having a mucoadhesive effect (Claim 34), from chemical, enzymatic, or physical inactivation as it passes through the stomach toward targeted release in the intestine. Otherwise, the active peptides or proteins embedded in the mucoadhesive polymer would be destroyed or inactivated in the stomach (Spec., p. 4, ll. 4-18). The outer coating is designed to dissolve only under the specific conditions (e.g. pH) presented in the intestine. When the outer layer is ultimately dissolved in the intestine, the inner matrix layer consisting essentially of the active substance and the

mucoadhesive is released, and the mucoadhesive binds the active substance to the intestinal mucosa, i..e., the mucus or mucin in the intestine (Spec., p. 6, ll. 6-19).

In the intestine, the mucoadhesive matrix bound to the intestinal mucosa provides superior distribution, bioavailability, and release of the active substance to the intestine in comparison to prior art bioadhesive matrices which bond directly to, are fixed on, and retained by the intestinal membrane itself (Spec., p. 6., l. 35, to p. 7, l. 3; p. 33, l. 24, to p. 34, l. 18). Moreover, because mucoadhesives bind to the mucus or mucin associated with the mucosal membrane and not the mucosal membrane itself, the mucoadhesives do not present a serious risk of the detrimental side effects known to be associated with prior art bioadhesive matrices that bind and stay bound to the mucosal membrane for sustained periods of time (Spec., p. 33, l. 24, to p. 34, l. 11). Mucoadhesives are readily and repeatedly flushed from the intestine. Bioadhesives are strongly bound to the mucosal membrane itself and cannot be readily eliminated.

GROUNDS OF REJECTION TO BE REVIEWED

A. The rejection of Claims 1, 3, 4, 6-11, and 34 under 35 U.S.C. §103 over Watts (U.S. Patent No 6,465,626, issued October 15, 2002). Claims 1, 3, 4, and 6-11 must be separately considered from Claim 34.

B. The rejection of Claims 1, 3, 4, 6-11, and 34 under 35 U.S.C. §103 over Watts in view of Berliner (U.S. Patent No. 5,849,327, issued December 15, 1998). Claims 1, 3, 4, and 6-11 must be separately considered from Claims 34-35.

C. The rejection of Claims 1, 3, 4, 6-11, and 34 under 35 U.S.C. §103 over Watts in view of Engel (U.S. Patent No. 5,773,032, issued June 30, 1998). Claims 1, 3, 4, and 6-11 must be separately considered from Claim 34.

D. The rejection of Claim 34 under 35 U.S.C. §102 as anticipated by Shimono (EP1203590 A1, published May 8, 2002).

E. The rejection of Claims 1, 4, 33 and 34 under 35 U.S.C. §103(a) over Shimono in view of Watts. Claims 1, 4, and 33 must be separately considered from Claim 34.

F. The rejection of Claims 1, 4, 9, 10, and 33-35 under 35 U.S.C. §103 over Shimono in view of Watts and Engel. Claims 1, 4, 9, 10, and 33 must be separately considered from Claims 34-35.

G. The rejection of Claim 34 under 35 U.S.C. 112, 1st ¶, for lack or written description.

H. The rejection of Claim 33 under 35 U.S.C. 112, 1st ¶, for lack or written description.

ARGUMENT

1. Introduction

All evidence upon which Applicant relies in this Appeal Brief was previously relied upon, and all arguments presented in this Appeal Brief were previously presented, in an earlier Appeal Brief filed May 4, 2009. Having considered Applicant's first Appeal Brief, the Examiner REOPENED prosecution and entered new grounds of rejection relating primarily to appealed Claim 35 (Claims Appendix, Claim 35). In the Office Action dated June 22, 2009 (OA), the Examiner stated (OA, p. 2, ¶2), "The grounds of rejection remain primarily the same as those previously applied but claim 35 was not properly rejected in the previous office action."

In the Evidence Appendix, under Other Evidence, Applicant again cites and attaches Shaheen et al., "Effect of Bio-adhesive Polymers like HPMC, Gelatine, Na-CMC and Xanthan Gum on Theophylline Release from Respective Tablets," International Journal of

Pharmacology, Vol. 2(5), pp. 504-508 (2006). The reference has been continually cited for its definition of the term bioadhesive and its recognition that gelatin is a non-erodable bioadhesive. Shaheen teaches (Shaheen, p. 504, col. 1; citations omitted; emphasis added):

> The term bio-adhesive describes materials that bind to biological substrate such as, mucosal membrane. Adhesion of bio-adhesive drug delivery devices to mucosal membrane leads to an increased drug concentration gradient at the adsorption site and therefore improved bioavailability of systematically delivered drugs. In general terms, adhesion of polymers to tissues may be achieved by (i) physical or mechanical bonds, (ii) primary or covalent chemical bonds and/or (iii) secondary chemical bonds (i.e., ionic). Physical or mechanical bonds can result from deposition and inclusion of the adhesive material in the crevices of the mucus or the folds of the mucosa. Secondary chemical bonds, contributing to bio-adhesive properties, consist of dispersed interactions (i.e., Van der Waals interactions) and stronger specific interactions, which include hydrogen bonds.

Shaheen's Figure 4 (Shaheen, p. 507, col. 2, Fig. 4) shows that gelatin is a bioadhesive which releases increasing percentages of theophylline for at least 8 hours. Shaheen concludes (Shaheen, pp. 507-508, bridging ¶; emphasis added):

> Bio-adhesive polymers like . . . Gelatin . . . were evaluated in sustaining the drug release from their respective tablets. . . . Gelatin also showed concentration dependent TH release . . . .

Shaheen distinguishes bioadhesive materials such as gelatin which chemically bind to the mucosal membrane from mucoadhesive materials that physically bind to the mucus or mucin (Shaheen, p. 504, col. 1). Note that the active peptide or protein in the inner matrix layer of appealed Claim 1 is physically embedded in a mucoadhesive polymer having a mucoadhesive effect.

To corroborate Shaheen's disclosure, Applicant also previously cited and submitted WO 93/13753, published July 22, 1993, including an English Abstract thereof, on a Form PTO 1449 (AP) for the Examiner's consideration and discussed the prior art teaching in the first Appeal Brief. The Examiner acknowledged consideration of the reference on April 21, 2008, in an Office Action dated April 30, 2008. The English Abstract of WO 93/13753 reads in its entirety (emphasis added):

> Described are pellets containing peptide drugs incorporated in a matrix consisting of gelatin or fractionated gelatin and plasticizers, the pellets having a semi-solid to gel-like consistency. Such drug forms exhibit, after application, bioadhesive properties and, by virtue of the matrix materials specified, allow or enhance the resorption of the peptide drug by the body.

2. Claim interpretation

The pellets of the oral multiparticle pharmaceutical form Applicant claims comprise (1) an "inner matrix layer consisting essentially of a mucoadhesive polymer having a mucoadhesive effect, in which is embedded an active substance which is a peptide or a protein" (Claims Appendix, Claim 1), and (2) an "inner matrix comprising 40 wt.% or less of an active pharmaceutical ingredient and a polymer having a mucoadhesive effect" (Claims Appendix, Claim 34). In both claims, the mucoadhesive polymer exhibits a mucoadhesive effect of at least η_b = 150 to 1000 mPa·s and a water uptake of from 10 to 750% in 15 min within +/- 0.5 pH units of the pH at which the outer coating starts to dissolve in the intestine (Claims Appendix, Claims 1 and 34).

Mucoadhesive properties and parameters are defined in the Specification at page 12, line 26, to page 13, line 15). As claimed, the "inner matrix layer" consists essentially of the active substance embedded in a mucoadhesive polymer "having a mucoadhesive effect" (Claim 1), or the "inner matrix" comprises the active ingredient and a polymer "having a mucoadhesive effect" (Claim 34). The transitional phrase "consisting essentially of" in Claim 1 closes the inner matrix layer of Claim 1 to materials or steps that materially affect the basic and novel characteristics of the claimed invention as a matter of law. *In re Herz*, 537 F.2d 549, 551-52 (CCPA 1976). The inner matrix comprising "a polymer having a mucoadhesive effect" of Claim 34 is functionally closed to matrix-forming materials in amounts which change the polymer having a mucoadhesive effect into a polymer NOT having a mucoadhesive effect. It is unreasonable in light of the invention disclosed in Applicant's Specification to inconsistently interpret the "inner matrix" of Claim 34 to read on

an inner matrix which does not include a polymer which has and exhibits "a mucoadhesive effect" in the inner matrix. Such an interpretation would be inconsistent with the teaching in Applicant's Specification as a whole and improper.

Moreover, it would be unreasonable to interpret the phrase "inner matrix comprising . . . an active pharmaceutical ingredient and a polymer having a mucoadhesive effect" (Claim 34) to broadly encompass inner matrices which do not contain the active ingredient as described in Shimono. A conclusion that the phrase "inner matrix comprising . . . an active pharmaceutical ingredient and a polymer having a mucoadhesive effect" (Claim 34) reads a core active ingredient coated with a water-insoluble polymer having a chitosan powder dispersed therein which Shimono appears to exclusively describe is unreasonable. Finally, a conclusion that the claimed form comprising pellets comprising an "inner matrix" and an "outer coating" reads on the inner matrix itself is most unreasonable.

3. The Examiner erred rejecting Claims 1, 3, 4, 6-11, and 34 under 35 U.S.C. § 103 in view of Watts

The Examiner erred rejecting Claims 1, 3, 4, 6-11, and 34 under 35 U.S.C. § 103 over Watts. The rejections should be reversed.

First, the patentability of Claims 1, 3, 4, and 6-11 over Watts should be separately considered from the patentability of Claim 34 over Watts because the "inner matrix layer" of Claim 1 consists essentially of an active peptide or protein substance embedded in a mucoadhesive polymer having a mucoadhesive effect while the "inner matrix" of Claim 34 comprises an active ingredient and a polymer having a defined mucoadhesive effect. Nevertheless, in both Claim 1 and Claim 34, the inner matrix must include a polymer "having a mucoadhesive effect". The evidence of record shows that bioadhesive polymeric mixtures which comprise minor amounts of chitosan do not comprise a polymer "having a mucoadhesive effect".

The evidence of record shows that mucoadhesive polymers bind to mucus or mucin associated with the mucosal membrane whereas bioadhesive matrices bind to the mucosal membrane itself. See Shaheen, page 504, column 1 (Evidence Appendix, Other Evidence)(attached) and Applicant's Specification at page 6, lines 10-19; page 6, line 35, to page 7, line 3; and page 33, line 24, to page 34, line 18. Because mucoadhesive polymers or polymers having a mucoadhesive effect bind to mucus or mucin and bioadhesive polymers or polymers having a bioadhesive effect bind to the mucosal membrane, the distribution, bioavailability, and release rate of the active substances embedded in or carried by the respective polymers are significantly different and would have been recognized by persons having ordinary skill in the art to be significantly different.

While the distribution and bioavailability of active substances from mucoadhesive polymers differ greatly from the distribution and bioavailability of active substances from bioadhesives, nevertheless, the greatest difference between the two distinct kinds of polymeric carriers is seen in the ability of the body to regularly flush the polymer carrier for the active substance from the body. Applicant's Specification teaches that there is a significant risk of side effects associated with bioadhesive substance carriers which bind strongly and continuously to internal tissue such as the mucosal membrane and thus cannot be readily eliminated from the body. The risk of side effects using bioadhesive carriers is substantial. On the other hand, mucoadhesive substance carriers do not bind to internal tissue such as the mucosal membrane. Rather, they bind to the mucus or mucin associated with the mucosal membrane. Therefore, they are readily and regularly eliminated or flushed from the body thereby reducing the risks of irritation and/or infection.

Applicant recognized that the different kinds of binding by mucoadhesives and bioadhesives and the comparatively reduced strength of binding by mucoadhesives also reduce the risk of toxicity from prolonged exposure to the active substance in the polymer

carrier. Mucoadhesives are bound to the mucus or mucin rather than to the mucosal membrane. Therefore, mucoadhesives are regularly removed or flushed along with the mucus or mucin and thus have a much shorter residence time in the body than bioadhesives that bind and remain bound to the body's mucosal membranes for substantial periods of time. Mucoadhesive pellets/particles that physically bind to mucus/mucin do not present the risk of toxicity presented by bioadhesive particles which are chemically bound to membrane tissue for periods of at least 8 hours. See Shaheen, p. 507, Fig. 4). Moreover, the distribution and bioavailability of substances bound to mucus or mucin is improved because the carrier is not fixed to any specific tissue at any specific site.

For example, bacteria that regularly binds to mucus do not have bioadhesive properties and therefore can be and are regularly washed from the intestine and eliminated or flushed. If bacteria had bioadhesive retention properties, the danger of infection would be severe. The mucoadhesive properties of the claimed oral multipariculate pharmaceutical form limit the residence time of the pharmaceutical agents in the intestine and their toxicity and side-effects, while the use of bioadhesive materials such as gelatin and compositions comprising substantial amounts of gelatin tend to increase the body's exposure time to the active substance and greatly increase the risk of side-effects. Bioadhesive materials are not readily and regularly eliminated from the body. Mucoadhesive materials are readily and regularly eliminated from the body with the mucous. Thus Applicant's claimed invention not only provides excellent distribution and bioavailability of the active ingredient in the intestinal lumen (Spec., p. 33, ll. 29-30) but does so without serious risks of toxicity, irritation, and infection (Spec., p. 33, l. 35, to p. 34, l. 11).

The present invention comprises pellets which provide targeted release of a mucoadhesive inner matrix including an active ingredient and a mucoadhesive polymer which adheres to the mucus or mucin in the intestine. Watt's pellets provide for targeted

release of a bioadhesive inner matrix which binds to the mucosal membranes rather than mucous. Watts itself acknowledges that the inner matrix of its delivery composition is a bioadhesive material and its microspheres are bioadhesive microspheres (Watts, Abstract). The evidence of record as a whole supports that view.

Watts discloses (Watts, col. 2, l. 67, to col. 3, l. 11):

> We have now found, surprisingly, that microparticles, produced from a combination of a chitosan and a cationic type A gelatin, possess particularly advantageous properties, which enable the improved transport of therapeutic agents . . . across mucosal surfaces . . . .
>
> Thus, according to a first aspect of the invention there is provided a composition comprising a mixture of chitosan and type A. cationic, gelatin, together with a therapeutic agent . . . .

Watts also teaches that the microparticles comprising chitosan, gelatin, and therapeutic agent may be coated with enteric polymers that do not dissolve in the acidic conditions in the stomach and prevent release of the therapeutic agent until the formulation reaches the intestine (Watts, col. 7, ll. 10-45).

However, Watts additionally teaches (Watts, col. 5, ll. 43-51):

> The microparticles will consist of preferably between 50 to 95%, or preferably between 70 and 90% and most preferably between 75 and 85% of the type A gelatin, and correspondingly between 50 and 5%, preferably between 30 and 10% and most preferably between 25 and 15% of chitosan . . . .

Most importantly, Watts found (Watts, col. 4, ll. 1-9):

> [T]he compositions according to the invention . . . provide for improved transport of polar drugs across, or for the improved presentation of vaccines to the mucosal surfaces . . . to such an extent that the effect is superior to that obtained for a chitosan solution, or microparicles produced from chitosan or type A gelatin alone . . . .

Watts explains just what is meant by "improved presentation" at column 7, lines 2-4 (emphasis added): "The compositions may gel on the mucosa at least to some extent and this may facilitate retention of the composition on the mucosa."

Accordingly, Watts teaches that its combination of at least 50% gelatin and at most 50% chitosan, preferably 70 to 90% gelatin and 30 to 10% chitosan, gels on the mucosal

membrane at least to some extent, helps retain the composition on the mucosa, and improves and prolongs the presentation of the active substance to the mucosal surfaces to an extent and effect superior to that produced by either chitosan or gelatin alone. What this means is that Watts' combination of at least 50% gelatin and at most 50% chitosan, preferably 70 to 90% gelatin and 30 to 10% chitosan, binds to and is retained by the mucosal surface to an extent superior to gelatin itself and therefore must have an overall bioadhesive effect. Thus, persons having ordinary skill in the art would have understood from Watts' teaching that the combination of at least 50% gelatin and at most 50% chitosan, preferably 70 to 90% gelatin and 30 to 10% chitosan, is not a mucoadhesive polymer, does not comprise a polymer having a mucoadhesive effect, and presents a substantial risk of toxicity and side effects such as irritation and infection. These are the precise effects Applicant's invention was designed to rectify and eliminate.

Watts' results are precisely the kind of results persons having ordinary skill in the art would have expected given the disclosure in the English Abstract of WO 93/13753, published July 22, 1993, that a matrix of gelatin or fractionated gelatin exhibits "bioadhesive properties". Moreover, Watts' results are corroborated by Shaheen's teaching that gelatin is a bioadhesive polymer which binds to the mucosal membrane, is retained by the mucosal membrane, and presents Theophylline to the mucosal membrane continuously for at least 8 hours.

Watts does not disclose Applicant's claimed pellets comprising an inner matrix layer consisting essentially of a mucoadhesive polymer having a mucoadhesive effect or an inner matrix comprising a polymer having the defined mucoadhesive effect. No composition Watts discloses or reasonably suggests includes a polymer or polymer composition which has "a mucoadhesive effect". To the contrary, the inner matrix of the microparticles disclosed by Watts does not consist essentially of an active substance and a mucoadhesive polymer and

does not comprise a polymer having a mucoadhesive effect. No polymer in Watts' compositions have a mucoadhesive effect. Watts teaches that its combination of at least 50% gelatin and at most 50% chitosan binds to, and is retained by, the mucosal surface to an extent superior to either gelatin or chitosan alone (Watts, col. 4, ll. 1-10).

When not combined with gelatin, chitosan does exhibit mucoadhesive properties, i.e., it binds to the mucus or mucin or the intestinal mucosa, and releases the active substance dispersed therein in the vicinity of the mucosal membrane (Spec., pp. 12-13, bridging ¶; pp. 33-34, bridging ¶). However, when combined with gelatin, chitosan does not exhibit mucoadhesive properties and does not have a mucoadhesive effect. Rather, when combined with gelatin, chitosan appears to have bioadhesive properties and binds to the mucosal membrane. Applicant's Claim 1 requires that the "mucoadhesive matrix layer is exposed and binds to the intestinal mucosa and releases the active substance there" (Claims Appendix, Claim 1). Both Claims 1 and 34 require the presence of a polymer having a mucoadhesive effect in the inner matrix of each pellet.

Gelatin is a bioadhesive polymer. It is the main component of Watts' inner matrix. By definition, bioadhesive compositions bind to the mucosal membrane. Shaheen, page 504, column 1. This has the disadvantage that the particles are retained by the mucosal membrane for substantial periods of time. This type of binding causes toxicity, irritation and other unwanted pharmacological side effects. The addition of at least 50% gelatin appears to not only reduce but to negate the mucoadhesive properties of chitosan and their benefits in Watts' compositions. Watts teaches that the binding properties of its compositions and their retention in the intestine are superior to gelatin itself (Watts, col. 4, ll. 1-10).

Applicant's Claim 1 requires an inner matrix layer "consisting essentially of" mucoadhesive components and requires the release of the active substance when the "mucoadhesive matrix layer is exposed and binds to the intestinal mucosa and releases the

active substance there" (Claims Appendix, Claim 1). Applicant's Claim 34 requires an inner matrix "comprising" an active ingredient and "a polymer having a mucoadhesive effect of at least η_β of 150 to 1,000 mPa·s and a water uptake ranging from 10 to 750% in 15 min at a pH between 5.5 and 7.2" (Claims Appendix, Claim 34). Watts teaches, and reasonably would have suggested, nothing of the kind.

The present invention not only recognizes but avoids the disadvantageous effects of Watts' invention. Unlike Watts' compositions, Applicant's mucoadhesive compositions bind to the mucus and can be washed away after releasing the active ingredient by the natural, on-going, renewal of the mucus layer. A visual depiction representative of the bioadhesive binding properties of gelatin to the glycocalyx membrane is provided in Figure 3 of WO 93/13753, of record.

The Examiner has not established that any invention Applicant claims would have been obvious to a person having ordinary skill in the art in view of Watts' disclosure. Watts does not recognize the problems associated with the use of strong mucosal membrane-binding bioadhesive polymers comprising gelatin and appears to have no interest whatsoever in reducing the binding capacity of its bioadhesive compositions for any reason. To the contrary, Watts would have led persons having ordinary skill in the art to believe that the stronger and longer the bioadhesive binds to the mucosal membrane the better. Watts leads persons having ordinary skill in the art away from Applicant's invention. As said in *KSR Int'l Co. v. Telflex Inc.*, 550 U.S. 398, ___ (2007), "[W]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious."

Accordingly, the Examiner's rejection of Claims 1, 3, 4, 6-11, and 34 under 35 U.S.C. § 103 over Watts should be reversed.

4. The Examiner erred rejecting Claims 1, 3, 4, 6-11, and 34 under 35 U.S.C. § 103 in view of Watts in view of Berliner

Claims 1, 3, 4, 6-11, and 34 stand rejected under 35 U.S.C. §103(a) over Watts in view of Berliner (U.S. Patent No. 5,849,327, issued December 15, 1998). The rejections should be reversed.

Berliner is cited by the Examiner for its teaching with regard to the outer coating thickness. Berliner does not remedy any of the other deficiencies of Watts' disclosure. Berliner does not disclose or reasonably suggest a coating thickness appropriate for coating an inner matrix including an active peptide or protein ingredient and a mucoadhesive polymer having an mucoadhesive effect. Unless there is some suggestion, teaching, incentive, and/or motivation to combine Berliner's teaching with Watts' disclosure to produce an oral multiparticulate pharmaceutical form including pellets comprising an inner matrix consisting essentially of an active ingredient and a polymer having a mucoadhesive effect, there is insufficient factual basis for the rejections over the combined prior art disclosures. Accordingly, the rejections should be reversed.

5. The Examiner erred rejecting Claims 1, 3, 4, 6-11, and 34 under 35 U.S.C. § 103 in view of Watts in view of Engel

Claims 1, 3, 4, 6-11, and 34 stand rejected under 35 U.S.C. §103(a) over Watts in view of Engel (U.S. Patent No. 5,773,032, dated June 30, 1998). The rejections should be reversed.

Engel is cited by the Examiner for its disclosure of the active ingredient cetrorelix in a sustained release particulate form. However, Engel does not remedy the other deficiencies of Watts' disclosure. Engel does not disclose or reasonably suggest making and using pharmaceutical pellets comprising an inner matrix including cetrorelix and a mucoadhesive polymer having a mucoadhesive effect. Unless there is some suggestion, teaching, incentive,

and/or motivation to combine Engel's teaching with Watts' disclosure to produce an oral multiparticulate pharmaceutical pellets including an inner matrix comprising an active ingredient such as cetrorelix and a polymer having a mucoadhesive effect, there is insufficient factual basis for the rejections over the combined prior art disclosures. Moreover, neither Watts, Engel, nor any combination thereof, reasonably suggests preparing Applicant's claimed compositions using cetrorelix as the active ingredient with a reasonable expectation that cetrorelix would or could be made compatible with the other components of the claimed invention and released as required by Claim 1. Accordingly, the rejections should be reversed.

6. The Examiner clearly erred rejecting Claim 34 under 35 U.S.C. § 102 as anticipated by Shimono

Claim 34 stands rejected under 35 U.S.C. §102 as anticipated by Shimono (EP1203590, published May 8, 2002). The rejection is clearly erroneous and should be reversed.

Shimono teaches two kinds of medicament-containing solid materials. Shimono's first material is specific for releasing a medicament in the large intestine and comprises [0007; 0008; emphasis added]:

> [A] solid preparation containing chitosan powder, which can release the medicament specifically in the large intestine and control the release of the medicament in the large intestine . . . obtained by coating successively a medicament-containing solid material with (1) a water-insoluble polymer having a chitosan powder dispersed therein, and (2) an enteric polymer.

Shimono's second material can partly disintegrate in the stomach but disintegrates more quickly in the large intestine. It comprises a medicament-containing solid material coated "only with a water-insoluble polymer having a chitosan powder dispersed therein" [0007; 0008]. In both the first and second Shimono materials, a water-insoluble coating film consisting of chitosan and a water-insoluble polymer are formed "around the [medicament-

containing] core" [0027; emphasis added]. An enteric coating may be formed around the water-insoluble coating film [0027]. In neither material is the medicament-containing material ever embedded in the mucoadhesive chitosan as in Applicant's Claim 1. In neither material is the medicament-containing material ever combined with chitosan in an inner matrix as in Applicant's Claim 34.

Furthermore, Shimono teaches [0019; 0020]:

> [T]he compounding ratio of the chitosan powder to the water-insoluble polymer may be in any possible range, but preferably in the range of about 1:20 to about 20:1, more preferavly in the range of about 1:10 to about 10:1, and especially preferably in the range of about 1:4 to about 4:1.

The ratios reasonably suggest that the medicament in the medicament-containing core is not present in an inner matrix comprising the medicament and chitosan. Rather the medicament in Shimono's core appears to be separated from the chitosan in the inner matric by the water-insoluble polymer. Interpreted in light of Applicant's supporting Specification as it must be interpreted, the inner matrix of Applicant's claimed form must comprise and include both the active substance and chitosan. Shimono neither describes nor suggests that the two active materials may be combined in a single inner matrix layer.

To the contrary, Shimono's construct does not conform to the configuration of the claimed invention. Shimono's water insoluble polymer layer not only contains dispersed chitosan particles, but it separates the "medicament-containing solid material" containing the medicament (acetaminophen) from the chitosan. Shimono's Figure 11 on page 21 which clearly shows that the chitosan particles are separated or isolated from the acetaminophen-containing layer and the outer enteric coating by the water-insoluble polymer.

Furthermore, the chitosan particles in Shimono composition are said to make the surface of the membranes of the large intestine more porous when they are decomposed by bacteria in the large intestine [0039]. This suggests that the chitosan particles bind to the

mucosal membrane and do not have a mucoadhesive effect in an inner matrix as Applicant's Claim 34 requires when combined with Shimono's water-insoluble polymer.

There is no evidence or suggestion in Shimono that either chitosan or the water-insoluble polymer, or any combination of chitosan and the water-insoluble polymer as combined in Shimomo's first coating, has or exhibits a mucoadhesive effect when combined in the ratios indicated. To the contrary, persons having ordinary skill in the art reasonably would have expected that, like the gel-forming, bioadhesive gelatin, hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, and xanthan gum matrices described in Watts, Shaheen, and WO 93/13753, Shimono's combination of water-insoluble polymers and chitosan would be more likely to exhibit bioadhesive binding characteristics.

In fact, chitosan's mucoadhesive characteristics appear to be negated when it is combined with Shimono's water-insoluble polymer. Persons having ordinary skill in the art reasonably would have understood from Shinono's disclosure that Shimono's water-insoluble polymer could not be readily eliminated or flushed from the intestine. Shimono's preparations are said to be "sustained release solid preparation[s] containing a chitosan powder" [0007; emphasis added]. Shimono's preparation "provides a sustained release solid preparation for producing the . . . colonic delivery solid preparation containing chitosan powder [0008]. Shaheen's materials, Watts' materials, and Shinomo's materials are all sustained release materials which retain a medicament-containing carrier in the intestine for substantial periods of time. Applicant's inner matrix comprising an active substance and a polymer having a mucoadhesive effect binds to the mucus or mucin. Thus, it is not retained in the intestine in solid form for substantial periods of time and would not be considered "a sustained release solid preparation". Bioadhesive materials are sustained release solid preparations.

In addition, because Shimono disperses chitosan in a water-insoluble polymer, the mixture will be very slow to dissolve in the intestine irrespective of the pH. Certainly, dissolution or disintegration of Shimono's water-insoluble polymer is unlikely to occur in Applicant's required 15 minutes at the neutral to acid intestinal pH levels specified in Applicant's Claim 34. Shimono's chitosan will be released from its water-insoluble polymer surrounds very slowly as are most sustained release solid preparations. That kind of sustained release is quite different from the release required for the claimed invention. Applicant's claims require chitosan exposure and binding to the mucus or mucin in a target area in 15 minutes at the pH presented in the intestine.

The PTO has the initial burden of proof to establish the factual basis for its rejection under 35 U.S.C. § 102. *In re Piasecki*, 745 F.2d 1468, 1472 (Fed. Cir. 1984). The PTO has not shown that Shimono describes every element of the subject matter defined by Applicant's Claim 34. Accordingly, the PTO's initial burden is not satisfied in this case, and the rejection of Claim 34 as anticipated by Shimono should be reversed.

7. The Examiner erred rejecting Claims 1, 4, 33, and 34 under 35 U.S.C. § 103 over Shimono in view of Watts

Claims 1, 4, 33, and 34 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Shimono in view of Watts. The rejections should be reversed.

Shimono is directed to a sustained release composition comprising a medicament-containing core which is coated with a water-insoluble polymer in which chitosan particles are dispersed. An outer layer of an enteric coating may be applied thereover.

On the other hand, Watts' invention is relates to pharmaceutical compositions with an inner matrix comprising an active substance, at least 50% gelatin, and no more than 50% chitosan (Watts, col. 4, l. 1, to col. 5, l. 51). The preponderance of the evidence of record shows that Watts' inner matrix does not consist essentially of an active substance and a

mucoadhesive polymer having a mucoadhesive effect as Claims 1 and 34 define and require. Rather, all the evidence of record strongly suggests that the mixture of gelatin and chitosan which forms Watts' inner matrix is a bioadhesive material which is bound to and retained by the mucosal membrane for substantial periods of time. Moreover, the preponderance of the evidence of record shows that Watts' inner matrix does not comprise an active substance and a polymer having a mucoadhesive effect of at least η_β of 150 to 1,000 mPa·s and a water uptake ranging from 10 to 750% in 15 min at a pH between 4.0 to 8.0 (Claim 1) or 5.5 to 7.2 (Claim 34). Thus, Watts neither describes nor reasonably suggests the subject matter Applicant claims.

The Office has not provided any evidence that either Watts' mixture of gelatin and chitosan or Shimono's mixture of a water-insoluble polymer and chitosan is a mucoadhesive polymer or comprises a polymer having, exhibiting, or providing a mucoadhesive effect in the composition which defines the inner matrix. Moreover, the Examiner has not established that there exists any common relationship or property between Watt's gelatin and Shimono's water-insoluble polymer which would have led persons having ordinary skill in the art to reasonably believe that any elements of Shimono's delivery compositions might or should be replaced by any elements of Watts' delivery compositions and vice versa with any reasonable expectation of making and using the delivery compositions Applicant claims. Rather, the Examiner summarily finds that chitosan is chitosan and thus inherently carries its mucoadhesive properties and benefits to any and all compositions including chitosan at all times. To the contrary, the evidence of record shows that the Examiner's finding is clearly erroneous.

Watts' delivery compositions comprising gelatin and chitosan appear to be bioadhesive compositions having a bioadhesive effect. Shimono's delivery compositions are sustained release compositions which make the mucosal membrane to which it is attached

porous when chitosan is degraded by bacteria. Watts, Shaheen, and the English Abstract of EP 93/13753, which were all previously cited during the prosecution below, instruct that gelatin and gelatin compositions containing chitosan have a bioadhesive effect rather than a mucoadhesive effect.

Moreover, unlike Watts' inner matrix in which the active substance is included in the composition of gelatin and chitosan, Shimono's chitosan particles are dispersed in a water-insoluble polymer and the water-insoluble polymer separates both the medicament-containing core from the chitosan particles and the chitosan particles from the enteric coating. See specifically Shimono's Figure 11. Furthermore, Shimono does not suggest including a peptide or protein medicament of the inner matrix, particularly the cetrorelix ingredient required in Applicant's Claims 6-8 and 35. Most importantly, however, neither Watts nor Shimono discloses an inner matrix core "consisting essentially of" the active ingredient and a mucoadhesive polymer having a mucoadhesive effect. Thus, there is no reasonable basis whatsoever in the combined prior art for rejecting Applicant's Claim 1 or any other claim dependent thereon as having been obvious to a person having ordinary skill in the art at the time Applicant's invention was made.

The Examiner points to no evidence which contradicts the evidence relied upon by Applicant in support of the patentability of its claims. Applicant's explanations of the differences between a mucoadhesive polymer such as chitosan and having a mucoadhesive effect and a bioadhesive polymer such as gelatin or mixtures of gelatin and chitosan and having a bioadhesive effect are firmly based in the evidence of record.

Accordingly, the Examiner's rejections of Claims 1, 4, 33, and 34 under 35 U.S.C. § 103 over Shimono in view of Watts should be reversed.

8. The Examiner erred rejecting Claims 1, 4, 9, 10, and 33-35 under 35 U.S.C. § 103 over Shimono in view of Watts and Engel

Claims 1, 4, 9, 10, and 33-35 stand rejected under 35 U.S.C. § 103 over Shimono in view of Watts and Engel. The rejection should be reversed.

The Examiner argues that it would have been prima facie obvious to a person having ordinary skill in the art to combine cetrorelix with chitosan in either Shimono's or Watts' delivery compositions. The problem with the Examiner's rationale is that no combination of Shimono and Watts would have led to the delivery compositions Applicant claims, and without some guidance, teaching, incentive, or motivation to combine cetrorelix with a mucoadhesive polymer having a mucoadhesive effect, persons having ordinary skill in the art would have had no reason to make and use Applicant's claimed multiparticulate pharmaceutical form with any reasonable expectation of success.

9. The Examiner erred rejecting Claim 34 under 35 U.S.C. § 112, 1st ¶

Claim 34 stands rejected under 35 U.S.C. 112, first paragraph, for lack of adequate written description in Applicant's Specification. The Examiner finds (OA, p. 4; emphasis added):

> Applicants have discussed that the composition may contain a lipophilic matrix . . . in which the active ingredient is embedded, which is then embedded in the matrix of the polymer with a mucoadhesive effect (see original claim 20). Applicants do not, however, disclose anything in regards to "a mucoadhesive lipophilic matrix embedded in the inner matrix" as the disclosure relates to a lipophilic matrix IN the mucoadhesive matrix. As the component has not been disclosed, the ingredient cannot be excluded from the compositions as claimed.

The Examiner's finding that Applicants do not disclose anything in regards to "a mucoadhesive lipophilic matrix embedded in the inner matrix" is clearly erroneous. At page 37, line 35, of the Specification, the paragraph is entitled "**Lipophilic matrix/polymers having a mucoadhesive effect**". A mucoadhesive lipophilic matrix clearly is disclosed in the Specification. More importantly, since its inclusion in the inner matrix is preferred

(Spec., pp. 37-38, bridging ¶), persons having ordinary skill in the art would have understood from the teaching of the Specification as a whole that the mucoadhesive lipophilic matrix may be embedded in the inner matrix or may be excluded from the inner matrix.

Therefore, the rejection of Claim 34 under 35 U.S.C. § 112, 1st ¶, for lack of written description should be reversed. The Examiner clearly erred finding no support for the term "mucoadhesive lipophilic matrix" or its exclusion from the inner matrix in the Specification.

10. The Examiner erred rejecting Claim 33 under 35 U.S.C. § 112, 1st ¶

Claim 33 stands rejected under 35 U.S.C. § 112, 1st ¶, for lack of written description in the Specification. The rejection should be reversed.

While the disclosure does not expressly describe a composition that does not contain gelatin in its inner matrix layer in those words, the Specification positively teaches that the claimed pellets may be packed into gelatin capsules (Spec., p. 33, ll. 19-22) and the Specification provides a wealth of examples of pellets wherein the inner matrix does not contain gelatin.

Ipsis verbis or a literal description of a claimed composition is not required in the Specification if it was clear that the Appellants had possession of the invention. A claim term need not be literally described in the Specification. See In re Kaslow, 707 F.2d 1366 (Fed. Cir. 1983):

> The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, **rather than the presence or absence of literal support** in the specification for the claim language (emphasis added).

Applicant's disclosure irrefutably shows that Applicant had possession of the claimed subject matter, including compositions wherein the inner matrix does not contain gelatin, at the time the Application was first filed. Therefore, the invention of Claim 33 is adequately

described in the supporting examples and the Specification as a whole. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991).

What then is the basis for the Examiner's rejection of Claim 33 when the express language of the claim is not required in the Specification, the supporting examples do not contain gelatin in the inner matrix, and persons having ordinary skill in the art would have understood that Applicant had possession of, and invented, the subject matter to which Claim 33 is directed at the time the Application was first filed. The basis for the Examiner's rejection is the Examiner's finding that the precise words used in Claim 33 do no appear in the Specification as filed. New words in the claims do not justify a finding of new matter therein. 35 U.S.C. § 112, 1st ¶, does not require the Specification to contain the precise words used in any claim.

Finally, gelatin is positively disclosed in the Specification exclusively for use in encapsulating the claimed pellets. Persons having ordinary skill in the art reasonably would have understood therefrom that gelatin may be excluded from every element of the claimed invention but the outermost encapsulating layer.

The Examiner's new matter rejection should be reversed.

RELIEF REQUESTED

For the reasons stated herein:

A. The rejection of Claims 1, 3, 4, 6-11, and 34 under 35 U.S.C. §103 over Watts (U.S. Patent No 6,465,626, issued October 15, 2002) should be REVERSED.

B. The rejection of Claims 1, 3, 4, 6-11, and 34 under 35 U.S.C. §103 over Watts in view of Berliner (U.S. Patent No. 5,849,327, issued December 15, 1998) should be REVERSED.

C. The rejection of Claims 1, 3, 4, 6-11, and 34 under 35 U.S.C. §103 over Watts in view of Engel (U.S. Patent No. 5,773,032, issued June 30, 1998) should be REVERSED.

D. The rejection of Claim 34 under 35 U.S.C. §102 as anticipated by Shimono (EP1203590 A1, published May 8, 2002) should be REVERSED.

E. The rejection of Claims 1, 4, 33 and 34 under 35 U.S.C. §103(a) over Shimono in view of Watts should be REVERSED.

F. The rejection of Claims 1, 4, 9, 10, and 33-35 under 35 U.S.C. §103 over Shimono in view of Watts and Engel should be REVERSED.

G. The rejection of Claim 34 under 35 U.S.C. 112, 1st ¶, for lack or written description should be REVERSED.

H. The rejection of Claim 33 under 35 U.S.C. 112, 1st ¶, for lack or written description should be REVERSED.

Applicant respectfully requests the Board to REVERSE all the appealed rejections.

Respectfully submitted,

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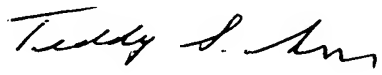
Norman F. Oblon



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CLAIMS APPENDIX

Claim 1 (Rejected): An oral multiparticulate pharmaceutical form comprising pellets having a size in the range from 50 to 2,500 μm, which comprise:

a) an inner matrix layer consisting essentially of a mucoadhesive polymer having a mucoadhesive effect, into which is embedded an active substance which is a peptide or a protein, which may include non-natural amino acid residue(s),

b) an outer film coating consisting essentially of an anionic polymer or copolymer,

wherein said multiparticulate pharmaceutical form is formulated so that

the contained pellets are released in the pH range of the stomach,

the outer coatings of the pellets are adjusted through the choice of the anionic polymer or copolymer or its formulation with excipients and its layer thickness such that the coating dissolves in pH ranges from 4.0 to 8.0 in the intestine within 15 to 60 min, so that the active substance-containing, mucoadhesive matrix layer is exposed and binds to the intestinal mucosa and releases the active substance there,

wherein the active substance content embedded in the matrix layer is a maximum of 40% by weight based on the weight of the polymer having a mucoadhesive effect, and

wherein the polymer having a mucoadhesive effect exhibits a mucoadhesive effect of η_b = 150 to 1000 mPa·s and a water uptake of from 10 to 750% in 15 min in a range of +/- 0.5 pH units relative to the pH at which the outer coating starts to dissolve and is selected from the group consisting of at least one of chitosan, a (meth)acrylate copolymer consisting of 20-40% by weight methyl methacrylate and 60 to 80% by weight methacrylic acid, a crosslinked polyacrylic acid, an uncrosslinked polyacrylic acid, an Na alginate, and a pectin.

Claim 2 (Withdrawn): The oral multiparticulate pharmaceutical form of claim 1, wherein the outer film coating is at least one material selected from the group consisting of

cellulose glycolate (Duodcell®), cellulose acetate phthalate (CAP, Cellulosi acetas, PhEur, cellulose acetate phthalates, NF, Aquaterie®), cellulose acetate succinate (CAS), cellulose acetate trimeliate (CAT), hydroxypropylmethylcellulose phthalate (HPMCP, HP50, HP55), hydroxypropylmethylcellulose acetate succinate (HPMCAS-LF, -MF, -HF), polyvinyl acetate phthalate (PVAP, Sureteric®), vinyl acetate-vinylpyrrolidone copolymer (PVAc, Kollidon® VA64), vinyl acetate:crotonic acid 9:1 copolymer (VAC:CRA, Kollicoat® VAC) and shellack.

Claim 3 (Rejected): The oral multiparticulate pharmaceutical form of claim 1, wherein the outer film coating consists of a (meth)acrylate copolymer having a content of monomers having anionic groups of from 5 to 60% by weight.

Claim 4 (Rejected): The oral multiparticulate pharmaceutical form of claim 1, wherein the layer thickness of the outer coating is in the range from 20 to 200 μm.

Claim 5 (Withdrawn): The oral multiparticulate pharmaceutical form of claim 1, further comprising a protease inhibitor and/or a penetration promoter.

Claim 6 (Rejected): The oral multiparticulate pharmaceutical form of claim 1, wherein the mucoadhesive polymer in the inner matrix is chitosan and the active pharmaceutical ingredient comprises Cetrorelix; and the outer coating comprises a copolymer of 50 wt% methylmethacrylate and 50 wt% methacrylic acid.

Claim 7 (Rejected): The oral multiparticulate pharmaceutical form of claim 6, wherein the inner matrix contains as polymer having a mucoadhesive effect a chitosan which

is employed together with an acid or a buffer system, which is located in the matrix or in or on a core onto which the matrix is applied.

Claim 8 (Rejected): The oral multiparticulate pharmaceutical form of claim 7, wherein the inner matrix layer contains chitosan and is adjusted to pH 5.0 to 5.5 by means of an acid or a buffer system, and is combined with an outer film coating which starts to dissolve in the range from pH 6.0 to 8.0.

Claim 9 (Rejected): The oral multiparticulate pharmaceutical form of claim 1, wherein the active substance is a protein or a peptide having an average molecular weight M_w of less than 3,000 Da.

Claim 10 (Rejected): The oral multiparticulate pharmaceutical form of claim 9, wherein the active substance is selected from the group consisting of abarelix angiogenesis II, anidulafungin, antide, argipressin, azaline and azaline B, bombesin antagonist, bradykinin, buserelin, cetrorelix, cyclosporin A, desmopressin, detirelix, encephalins (Leu-, Met-) ganirelix, gonadorelin, goserelin, growth hormone secretagogue, micafungin, nafarelin, leuprolide, leuprorelin, octreotide, orntide, oxytocin, ramorelix, secretin, somatotropin, terlipressin, tetracosactide, teverelix, triptorelin, thyroliberin, thyrotropin, vasopressin and mixtures thereof.

Claim 11 (Rejected): The oral multiparticulate pharmaceutical form of claim 9, wherein the inner matrix layer additionally contains a C_6- to C_{20}-fatty acid and/or a C_6- to C_{20}-alcohol including their salts, ether, ester or amide derivatives and/or a lipid and/or a phospholipid and/or a lipid-soluble vitamin.

Claim 12 (Withdrawn): The oral multiparticulate pharmaceutical form of claim 1, wherein the active substance is a protein or peptide having an average molecular weight M_w of from 3,000 to 10,000.

Claim 13 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 12, wherein the active substance is at least one substance selected from the group consisting of calcitonin, corticotrophin, endorphins, epithelial growth factor, glucagon, insulin, novolin, parathyroid hormone, relaxin, pro-somatostatin and salmon secretin.

Claim 14 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 12 wherein the matrix layer comprises a C_6- to C_{20}-alcohol including their salts, ether, ester or amide derivatives and/or a lipid and/or a phospholipid and/or a lipid-soluble vitamin and/or a protease inhibitor.

Claim 15 (Withdrawn): The oral multiparticulate pharmaceutical form of claim 1, wherein the active substance is a protein or peptide having an average molecular weight M_w of more than 10,000.

Claim 16 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 15, wherein the active substance is at least one substance selected from the group consisting of interferon (alpha, beta, gamma), interleukins (IL1, IL2), somatotropin, erythropoietin, tumor necrosis factor (TNF alpha, beta), relaxin, endorphin, dornase alpha, follicle stimulating hormone (FSH), human chorionic gonadotropin (HCG), human growth hormone release factor (hGRF), luteinizing hormone (LH) and epidermal growth factor.

Claim 17 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 15 wherein the matrix layer comprises a C_6- to C_{20}-fatty acid and/or a C_6- to C_{20}-alcohol including their salts, ether, ester or amide derivatives and/or a lipid and/or a phospholipid and/or a lipid-soluble vitamin and/or a protease inhibitor and/or a penetration promoter.

Claim 18 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 1, wherein a separating layer is applied between the active substance-containing matrix layer and the outer film coating layer.

Claim 19 (Withdrawn): A process for producing an oral multiparticulate pharmaceutical form as claimed in claim 1, comprising

a) producing an inner matrix layer comprising an active substance, which is a peptide or a protein, and a polymer having a mucoadhesive effect and, where appropriate, further pharmaceutically usual excipients by means of spray application onto a core or by rotagglomeration, precipitation or spray processes without a core, and subsequently,

b) applying an outer film coating consisting essentially of an anionic polymer or copolymer, which may optionally be formulated with pharmaceutically usual excipients, especially plasticizers, by means of spray application so that active substance-containing, enveloped pellets are obtained, and

c) processing the resulting pellets by means of pharmaceutically usual excipients in a manner known per se to a multiparticulate pharmaceutical form, in particular to pellet-containing tablets, minitablets, capsules, sachets or reconstitutable

powders, which are formulated so that the contained pellets are released in the pH range of the stomach.

Claim 20 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 1, wherein the active substance is embedded in a lipophilic matrix which has a melting point above 37°C, and the active substance-containing lipophilic matrix is embedded in the matrix composed of the polymer having a mucoadhesive effect.

Claim 21 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 20, wherein the active substance and the substance or substances forming the lipophilic matrix differ in their solubility in water according to DAB 10 and not more than +/- 50%, and/or differ in their partition coefficient according to annex V to directive 67/548/EEC, A.8 by not more than +/- 60%, and/or differ in their HLB measured by the method of Marszall not more +/- 80%.

Claim 22 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 20, wherein an active substance which has a solubility in water according to DAB 10 of at least 30 parts by volume of water for one part by weight of active substance is present.

Claim 23 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 22, wherein the active substance is at least one substance selected from the group consisting of peptide antibiotics, immunosuppressants, LHRH antagonists and immunomodulators.

Claim 24 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 22, wherein the active substance is at least one substance selected from the group consisting of abarelix, angiotensin II, anidulafungin, antide, argipressin, azaline and azaline B, bombesin antagonist, bradykinin, buserelin, calcitonin, cetrorelix, cyclosporin, cyclosporin A, desmopressin, detirelix, erythropoietin, encephalins (Leu-, Met-) ganirelix, gonadorelin, goserelin, growth hormone secretagogue, insulin, interferon (alpha, beta, gamma), interleukins (IL1, IL2), micafungin, nafarelin, leuprolide, leuprorelin, octreotide, orntide, oxytocin, parathyroid hormone, ramorelix, secretin, somatotropin, terlipressin, tetracosactide, teverelix, triptorelin, thyroliberin, thyrotropin, tumor necrosis factor (TNF alpha, beta) and vasopressin.

Claim 25 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 20, wherein the substance or substances forming the lipophilic matrix, and the polymer having a mucoadhesive effect either have the same ionic property or, in the event of opposed ionic properties, the polymer having a mucoadhesive effect is present in at least 50% neutralized form.

Claim 26 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 20, wherein the lipophilic matrix consists of 80 to 100% by weight of a substance having an HLB of from 0 to 15 or of a mixture of substances having an average HLB of from 0 to 15, and may comprise from 0 to 20% by weight of pharmaceutically usual excipients, stabilizers, thickeners or adsorbents.

Claim 27 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 20, wherein the substance or the substances forming the lipophilic matrix are at least

one substance selected from the group consisting of oils, fats, mono-, di- or triglycerides, fatty acids, fatty alcohols, especially C_6 to C_{20}-fatty acid and/or a C_6- to C_{20}- alcohol including their salts, ether, ester or amide derivatives, phospholipids, lecithins, emulsifiers, lipoids, lipid-soluble vitamins and surfactants.

Claim 28 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 20, wherein the lipophilic matrix comprises one of the following lipid preparations: (Imwitor 308) glyceryl monocaprylates having a monoester content of > 80%, (Imwitor 312) glyceryl monolaurates having a monoester content of > 90%, (Imwitor 491) glycerol monostearates (C_{16} + C_{18}) having a monoester content of > 90%, (Imwitor 900 P) glycerol monostearate having a monoester content of 40-55% and a C_{18} content of 40-60%, (Imwitor 900 K) glycerol monostearate, having a monoester content of 40-55% and a C_{18} content of 60-80%, (Imwitor 742) medium chain-length C_8 and C_{10} glycerides having a monoester content of 45-55%, (Imwitor 928) partial glycerides of saturated vegetable C_{10}-C_{18} fatty acids having a main content of C_{12}, and having a monoester content of 34-36%, C_8 and C_{10} glycerides, Na caprylate or Na capriate.

Claim 29 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 20, wherein the active substance is at least 10% soluble in the lipophilic matrix.

Claim 30 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 20, wherein the content of active substance-containing lipophilic matrix in the inner matrix layer a) is from 5 to 50% by weight.

Claim 31 (Withdrawn): A process for producing an oral multiparticulate pharmaceutical form as claimed in claim 20, comprising

a) producing the active substance-containing lipophilic matrix by suspending and/or dissolving the active substance with the substance(s) which form the lipophilic matrix and, where appropriate, further pharmaceutically usual excipients by vigorously mixing or melting the ingredients,

b) producing pre-pellets (pellet cores) by spray application of the mucoadhesive polymer mixed with the active substance-containing lipophilic matrix onto a core or by rotagglomeration, precipitation or spray processes without a core,

c) producing pellets by spray application of a coating of the anionic polymer or copolymer, which may optionally comprise admixtures of pharmaceutically usual excipients, especially plasticizers and release agents, from a dispersion or organic solution onto the pre-pellets from step b),

d) producing a multiparticulate pharmaceutical form by filling or incorporating the pellets from step c) in a manner known per se, where appropriate with use of pharmaceutically usual excipients, in particular by processing to pellet-containing tablets, minitablets, capsules, sachets or reconstitutable powders.

Claim 32 (Withdrawn): The process for producing an oral multiparticulate pharmaceutical form as claimed in claim 31, wherein steps a) and b) comprise

a) producing the inner matrix layer by preparing an emulsion, dispersion or solution of the active substance with the substance(s) for the lipophilic matrix, and where appropriate further pharmaceutically usual excipients by vigorously mixing the ingredients in water and producing an oil-in-water preparation having an average particle size of not more than 60 μm,

b) producing pre-pellets by spray application of the oil-in-water preparation from step a) onto the mucoadhesive polymer which may optionally comprise admixtures of further pharmaceutically usual excipients, where the ingredients are in the form of a micronized powder, by rotagglomeration, extrusion or granulation.

Claim 33 (Rejected): The oral multiparticulate pharmaceutical form of claim 1, which does not contain gelatin in the inner matrix layer.

Claim 34 (Rejected): A composition containing pellets ranging in size from 50 to 2,500 μm that comprise:

a inner matrix comprising 40 wt.% or less of an active pharmaceutical ingredient and a polymer having a mucoadhesive effect of at least η_β of 150 to 1,000 mPa·s and a water uptake ranging from 10 to 750% in 15 min at a pH between 5.5 and 7.2, and

an outer coating of anionic polymer or anionic copolymer;

wherein said particles do not have a layer separating the inner matrix and outer coating, and do not have a mucoadhesive lipophilic matrix embedded in the inner matrix;

wherein the outer coating dissolves at a pH ranging from 5.5 to 7.2 within 15 to 60 mins.

Claim 35 (Rejected): The composition of claim 34, wherein the mucoadhesive inner matrix comprises:

chitosan and the active pharmaceutical ingredient comprises Cetrorelix; and

the outer coating comprises a copolymer of 50 wt% methylmethacrylate and 50 wt% methacrylic acid.

CLAIM SUPPORT AND DRAWING ANALYSIS SECTION

There are no drawings associated with the Application on appeal.

Annotations showing support in the original claims or specification are **embolded** and indicated inside [**brackets**] below:

Claim 1: An oral multiparticulate pharmaceutical form [**claim 1, line 1**] comprising pellets having a size in the range from 50 to 2,500 μm [**claim 1, line 3**], which comprise:

a) an inner matrix layer [**claim 1, line 4**] consisting essentially of a mucoadhesive polymer having a mucoadhesive effect [**claim 1, lines 7-8, page 4, lines 26-32**], into which is embedded an active substance which is a peptide or a protein [**claim 1, line 5**], which may include non-natural amino acid residue(s) [**page 7, lines 14-15**],

b) an outer film coating [**claim 1 (b), page 58, lines 15-18; page 4, lines 34 *ff.*]**] consisting essentially of an anionic polymer or copolymer,

wherein said multiparticulate pharmaceutical form is formulated so that the contained pellets are released in the pH range of the stomach [**claim 1, page 58, line 24; page 5, lines 1-3**],

the outer coatings of the pellets are adjusted through the choice of the anionic polymer or copolymer or its formulation with excipients and its layer thickness such that the coating dissolves in pH ranges from 4.0 to 8.0 in the intestine within 15 to 60 min [**claim 1, page 58, lines 26-29; page 5, lines 5-10**], so that the active substance-containing, mucoadhesive matrix layer is exposed and binds to the intestinal mucosa and releases the active substance there [**claim 1, page 58, lines 31-33; page 5, lines 9-11**],

wherein the active substance content embedded in the matrix layer is a maximum of 40% by weight based on the weight of the polymer having a mucoadhesive effect [**claim 1, page 59, lines 1-3; page 6, lines 29-31**], and

wherein the polymer having a mucoadhesive effect exhibits a mucoadhesive effect of η_b = 150 to 1000 mPa·s [**claim 1, ; page 6, line 23**] and a water uptake of from 10 to 750% in 15 min in a range of +/- 0.5 pH units relative to the pH at which the outer coating starts to

dissolve [**claim 1, page 58, lines 34-37; page 6, line 26**] and is selected from the group consisting of at least one of chitosan, a (meth)acrylate copolymer consisting of 20-40% by weight methyl methacrylate and 60 to 80% by weight methacrylic acid, a crosslinked polyacrylic acid, an uncrosslinked polyacrylic acid, an Na alginate, and a pectin [**claim 6, page 60, lines 1-9; page 15-16, including table at top of page 16**] .

Claim 34: A composition containing pellets ranging in size from 50 to 2,500 μm [**claim 1, line 3; page 5, lines 25-30**] that comprise:

a inner matrix comprising 40 wt.% or less of an active pharmaceutical ingredient [**page 5, lines 13-19**] and a polymer having a mucoadhesive effect of at least η_β of 150 to 1,000 mPa·s and a water uptake ranging from 10 to 750% in 15 min at a pH between 5.5 and 7.2 [**page 15, lines 9-35**], and

an outer coating of anionic polymer or anionic copolymer [**page 16, line 6**];

wherein said **particles** do not have a layer separating the inner matrix and outer coating [**claim 18**], and do not have a mucoadhesive lipophilic matrix embedded in the inner matrix [**claim 20; page 37, line 35-page 38, line 12; page 34, line 20-page 35, line 31**];

wherein the outer coating dissolves at a pH ranging from 5.5 to 7.2 within 15 to 60 mins [**page 5, lines 7-8; page 6, lines 10-19**].

MEANS OR STEP PLUS FUNCTION APPENDIX

There are no claims with means or step plus function language on appeal.

EVIDENCE APPENDIX

Affidavits and Declarations

No secondary evidence in the form of an affidavit or declaration is relied upon in support of the finding and arguments in this appeal.

Other Evidence

Shaheen et al., "Effect of Bio-adhesive Polymers like HPMC, Gelatine, Na-CMC and Xanthan Gum on Theophylline Release from Respective Tablets," International Journal of Pharmacology, Vol. 2(5), pp. 504-508 (2006)(attached). The reference has been continually cited for its definition of the term bioadhesive and its recognition that gelatin is a non-erodable bioadhesive.

RELATED PROCEEDINGS APPENDIX

Appellant/Applicant, Appellant/Applicant's legal representative, and Appellant/Applicant's assignees, are aware of no appeals, interferences, or judicial proceedings that are related to, directly affect or would be directly affected by, or have a bearing on the Board's decision of the Board in this appeal.

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Effect of Bio-adhesive Polymers like HPMC, Gelatin, Na-CMC and Xanthan Gum on Theophylline Release from Respective Tablets

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Abstract: In order to evaluate the feasible application of bio-adhesive polymers like HPMC-15 cps and 50 cps; gelatin; Na-CMC and xantham gum in sustained release dosage form (SRDF), tablets containing various amount of bio-adhesive polymers with a model drug like anhydrous Theophylline sodium glycinate were prepared by compression in a hydraulic press (Perkin Elmer) compression machine using 5 ton pressure. The release characteristics of Theophylline (TH) from sustained release tablets were analyzed in triplicate using a thermal shaker (Memmert) with a shaking speed of 50 rpm at 37±0.5°C in 250 mL of simulated gastric fluid without enzyme for 8 h. At the end of 8 h of dissolution it was found that 61.60% (for 300 mg HPMC-15 cps) and 42.92% (for 500 mg HPMC-15 cps) of TH was released from HPMC-15 cps based tablets, respectively. When HPMC-15cps was increased to 50 cps, 52.12 and 59.66% of TH was released, respectively Both concentration and viscosity depended sustained release of TH was found. 74.13 and 94.15% of TH was released from Gelatin based SR tablets of the same concentrations, respectively. Gelatin also showed the same concentration effects i.e. release was reduced with an increase in concentration of polymer. 52.40 and 50.95% of TH was released from Na-CMC based SR tablets of the same concentrations, respectively and that of 76.96 and 78.26% of TH from xanthan gum based tablets. It means that there was no remarkable concentration effect of these two polymers on the TH release. In all cases there was almost zero order release fashion. Bio-adhesive polymers like HPMC and gelatin might be successfully applicable in SRDF rather than Na-CMC and xanthan gum studied here.

Key words: Bio-adhesive polymer, sustained release, dissolution, theophylline

INTRODUCTION

The term bio-adhesive describes materials that bind to biological substrate such as, mucosal membrane. Adhesion of bio-adhesive drug delivery devices to mucosal membrane leads to an increased drug concentration gradient at the absorption site and therefore improved bioavailability of systematically delivered drugs (Hannah, 2004). In general terms, adhesion of polymers to tissues may be achieved by (i) physical or mechanical bonds, (ii) primary or covalent chemical bonds and/or (iii) secondary chemical bonds (i.e., ionic). Physical or mechanical bonds can result from deposition and inclusion of the adhesive material in the crevices of the mucus or the folds of the mucosa. Secondary chemical bonds, contributing to bio-adhesive properties, consist of dispersive interactions (i.e., Van der Waals interactions) and stronger specific interactions, which include hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl (--OH) and the carboxylic groups (--COOH). Adhesive microspheres have been selected on the basis of the physical and chemical bonds formed as a function of chemical composition and physical characteristics, such as surface area.

This invention relates to a bio-adhesive tablet containing at least one bio-adhesive adjuvant and at least one lubricant, with at least one surface of the tablet comprising concentric or parallel, straight and/or curved depressions and to a method for producing the bioadhesive tablets as well as to pharmaceuticals in the form of the bioadhesive tablets. The bioadhesive tablets of the invention nearly completely release the active agent they contain and stimulate its resorption by the tissue while not entering into any undesirable with the biological tissue.

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The bioadhesive adjuvant should preferably be a substance that develops adhesion when coming into contact with the mucosa, such as hydroxypropyl methylcellulose (HPMC-15 and 50 cps), Sodium carboxymethyl cellulose (Na-CMC), gelatin, Xanthan gum. It is furthermore considered advantageous that the lubricant facilitates tabletting of cohesive mixtures as do talc, Mg-stearate.

The bio-adhesive tablets of the invention can be produced in a known way. Any active agent, especially medicinal substances, can be molded into tablets that adhere to the mucosa by adding a bioadhesive adjuvant, a lubricant and optionally other adjuvant common in tabletting using a simple technique. In the organism, the bioadhesive tablet is to adhere to the mucosa immediately upon contacting it, to develop as large a contact area as possible with the mucosa, while containing exclusively toxicologically safe adjuvants .

Xanthan gum, a hydrophilic polymer, was added to the formulation to increase the drug release. Changing the xanthan gum concentration as well as its particle size modified the *in vitro* drug release. Increasing xanthan gum concentrations yielded a faster drug release due to a higher liquid uptake, swelling and erosion rate (Verhoeven *et al.*, 2006).

Gelatin is a thermoreversible or cold-setting polymer. If the gelatin is not refrigerated or reheated, it will slowly convert back to a liquid. Because of this, a gelatin such as Jell-O® should remain refrigerated or it will become tasteless Kool-Aide®. Another popular dessert is Jell-O® instant pudding. It contains a modified food starch instead of gelatin. The instant pudding uses a heat-setting super absorbing thickening polymer (the starch) to create its gelatinous texture (PSLC, 2003). Gelatin and dextran were reported to blended and cross-linked hydrogels to form enzymatically degradable interpenetrating polymeric networks (IPNs) as materials for degradable implants (Kosmala *et al.*, 2000).

It was reported that a study of the erosion rates of matrices containing only indicated that Na-CMC (Belanose) eroded more quickly than HPMC (Dabbagh *et al.*, 1999).

Effect of incorporating pharmaceutical excipients on the in vitro release profiles and the release mechanism of monolithic hydroxypropylmethylcellulose (4000 cps) matrix tablets (m-HPMC tablets) in terms of mimicking the dual drug release character of bi-layered Tylenol ER tablets was studied. Release profiles and swelling rates of m-HPMC tablets were found to be highly influenced by the types and amounts of pharmaceutical excipients incorporated. The effect of pharmaceutical excipients on drug release from HPMC-based matrix tablets was found to be mainly due to a change in hydrophilic gel expansion and on physical interactions between the drug and HPMC (Cao *et al.*, 2005).

MATERIALS AND METHODS

Materials: Theophylline Na-Glycinate was a gift sample from Square Pharmaceuticals Bangladesh Limited. Sodium carboxymethylcellulose (Na-CMC), Xanthan gum, Gelatin and hydroxypropyl methylcellulose (HPMC, having a viscosity of 15 cps and 50 cps), were purchased from Loba Chemie Pvt. Ltd., India. Sodium chloride (Loba Chemie Pvt. Ltd., India.) were procured from commercial source. All other reagent used was of analytical grade.

Methodology: For tablet preparation, the amount of active ingredient is 100 mg and the total weight of tablet content was 406 and 609 mg. Theophylline Na-Glycinate, HPMC-15 and 50 cps, gelatin, Na-CMC, xanthan gum as a single bio-adhesive polymer, aerosil and Mg-Stearate were weighed separately (for 20 tablets) according to the formulations in Table 1 using a Mettler balance (AE--50, Switzerland) and mixed thoroughly in a drum blender mounted angularly ensuring thorough mixing. From this mixed mass, amount for individual tablet was weighed out and compressed into tablets in a hydraulic press (Perkin Elmer) compression machine using 5 ton pressure. Before compression, the surface of the die and punch was lubricated with magnesium stearate.

Table 1: The features of matrix tablets

Tablet code	No. of tablets	Drug (mg)	HPMC (15 cps) (mg)	HPMC (50 cps) (mg)	Gelatin (mg)	Na-CMC (mg)	Xanthan Gum (mg)	Aerosil (mg)	Mg. stearate	Total weight (mg)
F-1	20	100	300	-	-	-	-	4	2	406
F-1(a)	20	100	-	300	-	-	-	4	2	406
F-2	20	100	-	-	300	-	-	4	2	406
F-3	20	100	-	-	-	-	-	4	2	406
F-4	20	100	-	-	-	300	-	4	2	406
F-5	20	100	-	-	-	-	300	4	2	406
F-6	20	100	500	-	-	-	-	5	4	609
F-6(a)	20	100	-	500	-	-	-	5	4	609
F-7	20	100	-	-	500	-	-	5	4	609
F-8	20	100	-	-	-	-	-	5	4	609
F-9	20	100			-	500	-	5	4	609
F-10	20	100	-	-	-	-	500	5	4	609

***In vitro* dissolution study of tablets:** The release characteristics of Theophylline Na-Glycinate from sustained release tablets were supplied in triplicate using a thermal shaker (Memmert) with a shaking speed of 50 rpm at 37±0.5°C in 250 mL of simulated gastric fluid for 8 h. The dissolution samples were collected at a given interval (30 min), replaced with an equal volume of gastric fluid. The concentration of Theophylline Na-Glycinate release as a function of time was determined using an UV spectrophotometer (Shimadzu, Japan) at λ_{max} 271 nm.

Standard curve preparation: Standard Theophylline Na-Glycinate solution was prepared in the concentration range of 2-20 μg mL^{-1}. Then the absorbance of the standard solution of the different concentration were observed in the UV visible spectrophotometer (UV-1601, SHIMADZU, Japan) at λ_{max} 271 nm. From the observed absorbance, standard calibration curve was made for the assay of Theophylline Na-glycinate.

RESULTS AND DISCUSSION

Various theories have been elaborated in order to describe the process of release of the drug from matrices, by considering either diffusion (Armand *et al.*, 1987), in the case of non-erodable polymers, or erosion with erodable polymers (Bidah and Vergnaud, 1990).

Standard or working curve: A straight line was found when absorbance was plotted against concentration (Fig. 1). The slope value was found out from this straight line and used to calculate the drug concentration with proper volume corrections.

Effect of polymer (HPMC-15 cps) on the release of Theophylline from F-1 and F-6: The release profiles of Theophylline from F-1 and F-6 were shown in Fig. 2. F-1 contains 300 mg of HPMC-15 cps and F-6 contains 500 mg of HPMC-15 cps. About 5.81 and 1.52% of Theophylline released from F-1 and F-6, respectively after 30 min of dissolution period. After 4 h of dissolution period F-1 and F-6 released 38.32 and 20.08% of Theophylline respectively. At the end of 8 h of dissolution it was found that 61.60 and 42.92% of Theophylline have been released from F-1(a) and F-6(a) respectively. HPMC-15 cps is a hydrophilic gel forming agents. It is preferred the formulators to modulate drug release mainly due to its claim to form strong viscous gel in contact with water. It has been observed that the release of Theophylline decreased when the amount of polymer increased.

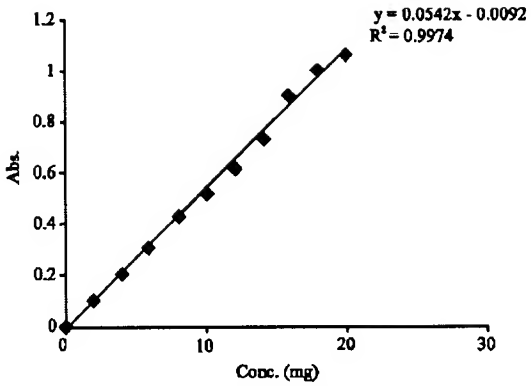

Fig. 1: Standard curve of theophylline Na-glycinate

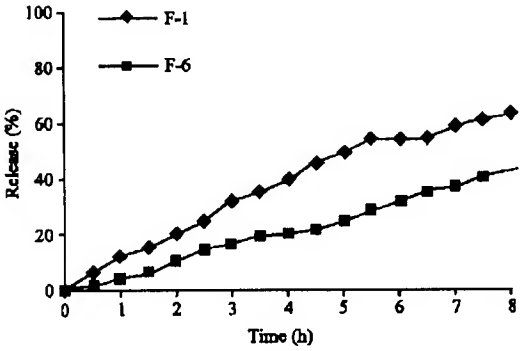

Fig. 2: Theophylline release profiles from HPMC-15 cps based tablets

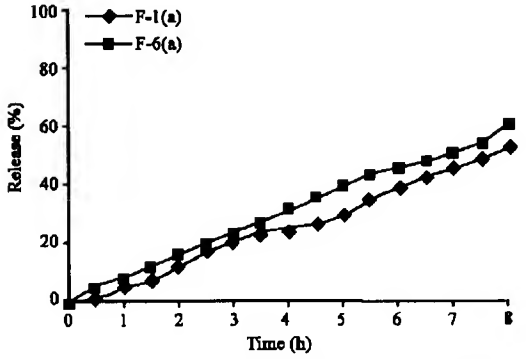

Fig. 3: Theophylline release profiles from HPMC-50 cps based tablets

Effect of polymer (HPMC-50 cps) on the release of Theophylline from F-1(a) and F-6(a): Tablets of F-1(a) and F-6(a) were prepared by the same process as described earlier. The release profiles of Theophylline from F-1(a) and F-6(a) were shown in Fig. 3. F-1(a) contains 300 mg of HPMC-50 cps and F-6(a) contains 500 mg of HPMC-50 cps. About 1.19 and 5.46% of Theophylline released from F-1(a) and F-6(a), respectively after 30 min of dissolution

period. After 4 h of dissolution period, F-1(a) and F-6(a) released 23.84 and 31.81% of Theophylline, respectively. At the end of 8 h of dissolution it was found that 52.12 and 59.66% of Theophylline have been released from F-1(a) and F-6(a), respectively.

Effect of polymer (Gelatin) on the release of Theophylline from F-2 and F-7: Tablets of F-2 and F-7 were prepared by the same process as described earlier The release profiles of Theophylline from F-2 and F-7 were shown in Fig. 4. F-2 contains 300 mg of Gelatin and F-7 contains 500 mg of Gelatin. About 1.43 and 3.33% of Theophylline released from F-2 and F-7, respectively after 30 min of dissolution period. After 4 h of dissolution period F-2 and F-7 released 57.87 and 69.14% of theophylline, respectively. At the end of 8 h of dissolution, it was found that 74.13 and 94.15% of theophylline have been released from F-2 and F-7, respectively.

Effect of polymer (Na-CMC) on the release of Theophylline from F-4 and F-9: Tablets of F-4 and F-9 were prepared by the same process as described earlier The release profiles of Theophylline from F-4 and F-9 were shown in Fig. 5. F-4 contains 300 mg of Na-CMC and F-9 contains 500 mg of Na-CMC. About 0.59 and 2.73% of Theophylline released from F-4 and F-9, respectively after 30 min of dissolution period. After 4 h of dissolution period F-4 and F-9 released 27.12 and 27.72% of Theophylline, respectively. At the end of 8 h of dissolution, it was found that 52.40 and 50.95% of Theophylline have been released from F-4 and F-9, respectively.

Effect of polymer (xanthan gum) on the release of Theophylline from F-5 and F-10: Tablets of F-5 and F-10 were prepared by the same process as described earlier. The release profiles of Theophylline from F-5 and F-10 were shown in Fig. 6. F-5 contains 300 mg of xanthan gum and F-6 contains 500 mg of Xanthan gum. About 1.19 and 3.99% of theophylline released from F-5 and F-10, respectively after 30 min of dissolution period. After 4 h of dissolution period F-5 and F-10 released 46.27 and 40.67% of theophylline, respectively. In case of F-10 after 6 h of dissolution period there is a vast release of active ingredient. At the end of 8 h of dissolution, it was found that 76.96 and 78.26% of Theophylline have been released from F-5 and F-10, respectively. It has been observed that there was no significant effect of drug release for the increase of polymer.

Release fashion: In almost all cases the release fashion i.e., % release vs. time curves were approximately straight lines, which approximates to the zero order release fashion.

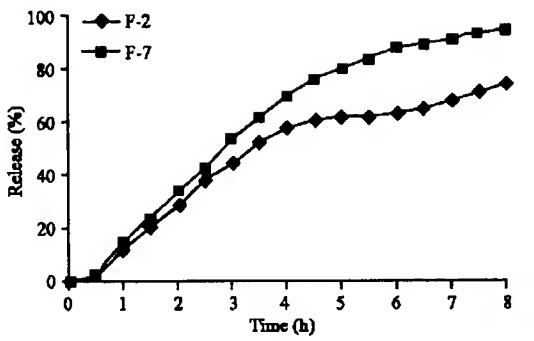

Fig. 4: Theophylline release profiles from gelatin based tablets

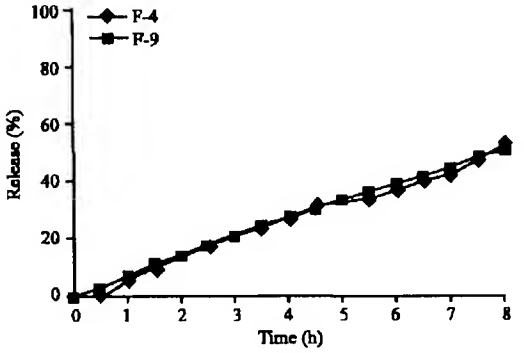

Fig. 5: Theophylline release profiles from Na-CMC based tablets

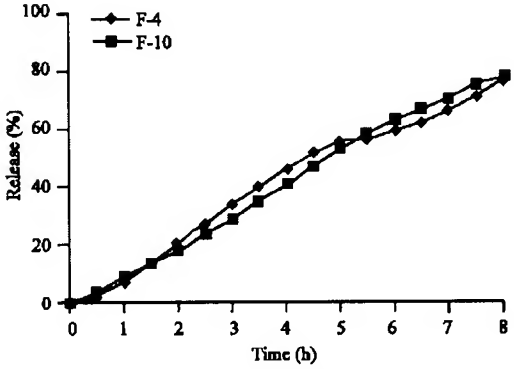

Fig. 6: Theophylline release profiles from xanthan gum based tablets

CONCLUSIONS

Bio-adhesive polymers like HPMC, Gelatin, Na-CMC and Xantham gum were evaluated in sustaining the drug release from their respective tablets. Both the HPMC showed the concentration as well as grade-dependent sustained release of TH. Gelatin also showed

concentration dependent TH release whereas Na-CMC and Xantham gum showed a very little dependency with sustaining the TH release. In all cases the release fashion was approximately zero order process. The potential application of HPMC with their different grades and Gelatin might be feasible in SRDF.

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